Axsome Therapeutics Announces Topline Results of the STRIDE-1 Phase 3 Trial in Treatment Resistant Depression and Expert Call to Discuss Clinical Implications

March 30, 2020

Achieves key secondary endpoints demonstrating rapid and statistically significant improvements in depressive symptoms on MADRS versus active comparator at Weeks 1, 2, and overall (key secondary endpoints, p=0.02, 0.035, and 0.031)

Demonstrated numerical improvement on primary endpoint (MADRS at Week 6) versus active comparator, but did not reach statistical significance (p=0.12)

Rapid and statistically significant remission of depression achieved versus active comparator starting at Week 1 (p=0.001, QIDS-SR-16)

Statistically significant improvement in cognitive function (p=0.011) and anxiety (p=0.009, HAM-A) versus active comparator

Data support continued development in TRD with initiation of second Phase 3 trial anticipated 3Q 2020

NDA filing for Breakthrough Therapy-designated AXS-05 in MDD on track for 4Q 2020

Topline results for ADVANCE-1 pivotal trial of AXS-05 in Alzheimer's disease agitation on track for early 2Q 2020

Company to host conference call with Dr. Maurizio Fava today at 8:00 AM ET

NEW YORK, March 30, 2020 (GLOBE NEWSWIRE) -- Axsome Therapeutics, Inc. (NASDAQ: AXSM), a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders, today announced that AXS-05, a novel, oral, investigational NMDA receptor antagonist with multimodal activity, met key secondary endpoints in the STRIDE-1 trial by rapidly and statistically significantly improving symptoms of depression on the Montgomery-Åsberg Depression Rating Scale (MADRS), as early as Week 1 and for the overall 6-week treatment period, as compared to the active comparator bupropion in patients with treatment resistant depression (TRD). The STRIDE-1 trial did not reach statistical significance on the Week 6 primary endpoint on MADRS. STRIDE-1 was a randomized, double-blind, active-controlled, multi-center, U.S. trial, in which 312 adult patients with confirmed TRD, who had failed two or three prior treatments, were randomized to treatment with either AXS-05 (45 mg dextromethorphan/105 mg bupropion) or 150 mg bupropion, twice daily for 6 weeks.

AXS-05 rapidly and significantly improved symptoms in patients with TRD as measured by MADRS averaged over the entire 6-week treatment period, a key secondary endpoint, with mean reductions of 8.6 for AXS-05 versus 6.7 for bupropion (p=0.031). The rapid onset of action with AXS-05 treatment was demonstrated with statistically significant mean MADRS reductions at Week 1, the earliest time point measured, of 5.2 versus 3.6 respectively for AXS-05 and bupropion (p=0.02), and at Week 2 of 8.0 versus 6.1 respectively for AXS-05 and bupropion (p=0.035), both time points being key secondary endpoints. At Week 6, the primary endpoint, AXS-05 demonstrated a numerically greater improvement in MADRS, with mean reductions of 11.6 for AXS-05 versus 9.4 for bupropion (p=0.117).

AXS-05 rapidly and significantly improved depressive symptoms in patients with TRD as measured by the Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16) averaged over the entire 6-week treatment period, with mean reductions of 3.3 for AXS-05 versus 2.3 for bupropion (p=0.013). Rates of remission from depression (defined as QIDS-SR-16 ≤5) were statistically significantly greater for AXS-05 compared to bupropion at Week 1 (p=0.001) and at every time point thereafter, being achieved by 18.2% of AXS-05 patients compared to 8.2% of bupropion patients at Week 6 (p=0.012).

AXS-05 significantly improved cognitive function in patients with TRD as compared to bupropion, assessed using the Cognitive subscale of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (p=0.011). Cognitive dysfunction is well documented in the different phases of major depression, and plays an important role in functional recovery from major depression. The improvement in cognitive function with AXS-05 was rapid as compared to bupropion, reaching statistical significance as early as Week 2 (p=0.01) and at every time point thereafter. The Cognitive subscale of the CPFQ assesses sharpness/mental acuity, and the ability to focus/maintain attention, to remember/recall information, and to find words. Statistical significance for the superiority of AXS-05 versus bupropion was also achieved for the entire CPFQ (p=0.014), which assesses physical in addition to cognitive functioning.

AXS-05 rapidly and significantly reduced anxiety symptoms in patients with TRD as compared to bupropion, assessed using the Hamilton Anxiety Scale (HAM-A) (p=0.009). AXS-05 demonstrated numerical improvement versus the active comparator bupropion for all other efficacy variables assessed.

"In patients with depression that is resistant to current treatments, AXS-05 demonstrated a rapid and clinically meaningful improvement in depressive symptoms and in cognitive function. The results with AXS-05 in this trial are especially notable in light of the well-known low level of response in treatment resistant depression, the use of an active comparator administered at a higher dose, and the administration of the active comparator for twice the duration of AXS-05 administration," said Professor Maurizio Fava, MD, Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, and Associate Dean for Clinical & Translational Research at Harvard Medical School. "The results of the STRIDE-1 trial add to the growing body of evidence for the anti-depressant effects of AXS-05, an NMDA receptor antagonist with multimodal activity. These data suggest that AXS-05 may represent a novel approach both for the frontline treatment of major depressive disorder, and for treatment resistant depression."

The positive findings with AXS-05 in patients with TRD build upon the rapid and statistically significant improvements in depressive symptoms in patients with MDD previously demonstrated in two pivotal trials, the ASCEND active-controlled trial and the GEMINI placebo-controlled trial. AXS-05 was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in March 2019. Based on the outcome of the FDA Breakthrough Therapy meeting, Axsome believes the positive results of the GEMINI and ASCEND trials are sufficient to

support submission of a New Drug Application (NDA) for AXS-05 for the treatment of MDD, as previously disclosed. Axsome remains on track to submit the NDA in the fourth quarter of 2020.

AXS-05 was well tolerated in the trial. The most commonly reported adverse events in the AXS-05 arm were dizziness and nausea. The rates of discontinuation due to adverse events were low in both treatment groups (2.6% for AXS-05 and 1.9% for bupropion). There were 3 serious adverse events in the AXS-05 arm, consisting of migraine; overdose; and suicidal ideation, which occurred more than one week after the cessation of treatment. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.

"These STRIDE-1 results provide the first evidence of clinical activity of AXS-05 in patients with treatment depression, an area of high unmet medical need. Although the primary endpoint at week 6 did not reach statistical significance, we are encouraged by the overall results as they continue to demonstrate a rapid, statistically significant onset of action for AXS-05 which, in this study, has translated through to even the most difficult-to-treat population," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "The differentiated profile of AXS-05 demonstrated in the STRIDE-1 trial, including rapid induction of remission, and positive effects on cognition and anxiety, support the continued development of AXS-05 in treatment resistant depression, and initiation of a second Phase 3 trial in this indication is anticipated in the third quarter. Separately, we remain on track to file an NDA in the fourth quarter for AXS-05 in the treatment of major depressive disorder, based on the previously completed positive GEMINI and ASCEND trials. We expect data readouts from our INTERCEPT Phase 3 trial of AXS-07 in early treatment of migraine imminently, and from our ADVANCE-1 Phase 2/3 trial of AXS-05 in Alzheimer's disease agitation in early second quarter."

"STRIDE-1 is now the third efficacy trial in which AXS-05 has demonstrated a rapid, statistically significant onset of action in patients with depression and it is the second trial against the active comparator bupropion in which AXS-05 has demonstrated statistically significant improvement in depressive symptoms," said Cedric O'Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. "The novel NMDA mechanism and multimodal action of AXS-05 may be especially relevant to patients with TRD given the growing evidence for the importance of glutamatergic modulation in depression. The observed improvements in both cognition and anxiety with AXS-05 are also noteworthy and expand AXS-05's therapeutic profile in CNS disorders."

Based on the results of the STRIDE-1 trial, Axsome intends to initiate a second Phase 3 trial of AXS-05 in patients with treatment resistant depression in the third quarter of 2020. Detailed study results, including additional secondary endpoints, will be submitted for presentation at upcoming medical meetings and for publication. AXS-05 is also being evaluated in the ADVANCE-1 trial in patients with Alzheimer's disease agitation. AXS-05 was granted Fast Track designations by the FDA for the treatment of TRD and for the treatment of Alzheimer's disease agitation.

Summary of Topline Results of the STRIDE-1 Trial

Effect on Depressive Symptoms

- AXS-05 was associated with a statistically significant mean reduction from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the entire 6-week treatment period (key secondary endpoint), with mean reductions of 8.6 for AXS-05 versus 6.7 for bupropion (p=0.031).
- AXS-05 was associated with a statistically significant mean reduction from baseline in the Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16) total score over the entire 6-week treatment period, with mean reductions of 3.3 for AXS-05 versus 2.3 for bupropion (p=0.013).
- Remission from depression (defined as QIDS-SR-16 ≤5) was statistically significantly greater for AXS-05 compared to bupropion, being achieved by 18.2% of AXS-05 patients compared to 8.2% of bupropion patients at Week 6 (p=0.012).

Time Course of Effect on Depressive Symptoms

- At Week 1 (key secondary endpoint), the earliest time point assessed, AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 5.2 versus 3.6 for bupropion (p=0.02).
- At Week 2 (key secondary endpoint), AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 8.0 versus 6.1 for bupropion (p=0.035).
- At Week 6 (primary endpoint), AXS-05 demonstrated a numerically greater improvement in MADRS, with mean reductions of 11.6 for AXS-05 versus 9.4 for bupropion (p=0.117).
- At Week 1, remission rates (defined as QIDS-SR-16 ≤5) were statistically significantly greater with AXS-05 versus bupropion (p=0.001), with statistical significance maintained at every time point thereafter.

Cognitive Function

- AXS-05 was associated with a statistically significant improvement in cognitive function in patients as compared to bupropion, assessed using the Cognitive subscale of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (p=0.011).
- The improvement in cognitive function with AXS-05 was rapid as compared to the active comparator bupropion, reaching statistical significance as early as Week 2 (p=0.01) and at every time point thereafter.

Anxiety Symptoms

- AXS-05 rapidly and significantly reduced anxiety symptoms as compared to bupropion, assessed using the Hamilton Anxiety Scale (HAM-A) (p=0.009).

Safety and Tolerability

- AXS-05 was well tolerated in the trial.
- The most commonly reported adverse events in the AXS-05 arm were dizziness and nausea. There were 3 serious adverse events in the AXS-05 arm, consisting of migraine; overdose; and suicidal ideation, which occurred more than one week after the cessation of treatment.
- The rates of discontinuation due to adverse events were low in both treatment groups (2.6% for AXS-05 and 1.9% for bupropion).
- Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.

Conference Call Information

Axsome will host a conference call and webcast with slides today at 8:00 AM Eastern to discuss the topline results of the STRIDE-1 trial of AXS-05 in treatment resistant depression. Professor Maurizio Fava, MD, Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, and Associate Dean for Clinical & Translational Research at Harvard Medical School will join the call and will be available to answer questions. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the passcode 4166236. The live webcast can be accessed on the "Webcasts & Presentations" page of the "Investors" section of the Company's website at axsome.com. A replay of the webcast will be available for approximately 30 days following the live event.

About the STRIDE-1 Trial

STRIDE-1 (Symptom Treatment in Resistant Depression 1) was a Phase 3, randomized, double-blind, active controlled trial to assess the efficacy and safety of AXS-05 in the treatment of treatment resistant depression (TRD). Patients with major depressive disorder (MDD) who had previously failed one or two antidepressant treatments were treated in an open-label fashion with 150 mg bupropion twice daily (300 mg total daily dose) (n=799) during a 6-week lead-in period. Patients who failed to respond to bupropion during this lead-in period were randomized in a 1:1 ratio to treatment with bupropion at this same total daily dose (n=156), or to treatment with AXS-05 (45 mg dextromethorphan/105 mg bupropion) twice daily (90 mg dextromethorphan/210 mg bupropion total daily dose) (n=156), for 6 weeks. The change in depressive symptoms over time was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16). The primary endpoint was the change from baseline in the MADRS after 6 weeks of treatment. The key secondary endpoints were the change from baseline in the MADRS after 1 week of treatment, after 2 weeks of treatment, the average change over entire 6-week double-blind treatment period, and the Sheehan Disability Scale (SDS). Other pre-specified secondary efficacy variables included the Cognitive subscale of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), and the Hamilton Anxiety Scale (HAM-A).

About Treatment Resistant Depression (TRD)

Patients diagnosed with major depressive disorder (MDD) are defined as having TRD if they have failed two or more antidepressant therapies. MDD is a serious condition characterized by depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and which impairs social, occupational, educational, or other important functioning. According to the National Institute of Health, an estimated 7.1% of U.S. adults experience MDD each year. Nearly two-thirds of diagnosed and treated patients do not experience adequate treatment response with first-line therapy, and the majority of these initial failures also fail second-line treatment.

About the Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a well-established, 10-item, validated rating scale used to provide an assessment of depression, and as a guide to evaluate recovery. This scale is an accepted regulatory endpoint for depression. The scale is used in clinical research to rate the severity of a patient's depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms.

About AXS-05

AXS-05 is a novel, oral, patent-protected, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of major depressive disorder and other central nervous system (CNS) disorders. AXS-05 consists of a proprietary formulation and dose of dextromethorphan and bupropion and utilizes Axsome's metabolic inhibition technology. The dextromethorphan component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, which is a novel mechanism of action, meaning it works differently than currently approved therapies for major depressive disorder. The dextromethorphan component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 is covered by more than 40 issued U.S. and international patents which provide protection out to 2034. AXS-05 has been granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy designation for the treatment of MDD as well as Fast Track designations for the treatment of treatment resistant depression and for the treatment of Alzheimer's disease agitation. AXS-05 is not approved by the FDA.

About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders for which there are limited treatment options. Axsome's core CNS product candidate portfolio includes four clinical-stage candidates, AXS-05, AXS-07, AXS-09, and AXS-12. AXS-05 is being developed for major depressive disorder (MDD), treatment resistant depression (TRD), Alzheimer's disease (AD) agitation, and for smoking cessation treatment. AXS-07 is being developed for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. AXS-14 is being developed for the treatment of fibromyalgia. AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 are investigational drug products not approved by the FDA. For more information, please visit the Company's website at axsome.com. The Company may occasionally disseminate material, nonpublic information on the company website.

Forward Looking Statements

Certain matters discussed in this press release are “forward-looking statements”. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials, and the number or type of studies or nature of results necessary to support the filing of a new drug application (“NDA”) for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, our product candidates (including, but not limited to, FDA’s agreement with the Company’s plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee’s recommendations); the potential for the MOMENTUM clinical trial to provide a basis for approval of AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment; the potential for the ASCEND clinical trial, combined with the GEMINI clinical trial results, to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs and collaborations; the success of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; the Company’s anticipated capital requirements, including the Company’s anticipated cash runway; unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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